Docket No.: 30694/41506
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Orit Kollet et al.

Application No.: 10/552,299 Confirmation No.: 2069

Filed: August 25, 2006 Art Unit: 1636

For: Stem Cells Having Increased Sensitivity to SDF-1 and Methods of Generating and Using Same Examiner: Shen, W.C.W.

RESPONSE TO RESTRICTION REQUIREMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

In response to the restriction requirement set forth in the Office Action mailed February 6, 2009, Applicants hereby provisionally elect the claims of Group IX, i.e., claims 30-36, 38, and 39, for continued examination. In response to the Office's requirement for election of species, Applicants elect MMP-2. Claims 30-36, 38, and 39 read on the elected species. Applicants respectfully traverse the requirement for restriction for the reasons set forth below.

The Restriction Requirement

The Examiner has required restriction between the following groups of claims:

Groups I and II: Claims 1-7 and 9, drawn to a method of increasing sensitivity of hematopoietic stem cells *in vitro* (Group I) or *in vivo* (Group II) to a chemoattractant, the method comprising exposing the stem cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

Groups III and IV: Claims 1-4, 8, and 9, drawn to a method of increasing sensitivity of mesenchymal stem cells *in vitro* (Group III) or *in vivo* (Group IV) to a

chemoattractant, the method comprising exposing the stem cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

Group V: Claims 10-16, drawn to an *in vivo* method of treating a disorder requiring cell or tissue replacement, the method comprising providing to a subject in need thereof a therapeutically effective amount of hematopoietic stem cells treated with a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells, thereby treating the disorder requiring cell or tissue replacement in the subject.

Group VI: Claims 10-13 and 17, drawn to an *in vivo* method of treating a disorder requiring cell or tissue replacement, the method comprising providing to a subject in need thereof a therapeutically effective amount of mesenchymal stem cells treated with a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells, thereby treating the disorder requiring cell or tissue replacement in the subject.

Group VII: Claims 18-21, drawn to a culture medium suitable for increasing the sensitivity of stem cells to a chemoattractant, the culture medium comprising a matrix metalloprotease or an active portion thereof which is capable of increasing a level of at least one chemoattractant receptor of the stem cells and a buffer solution suitable for stem cell culturing.

Group VIII: Claims 22-29, drawn to a method of using a matrix metalloprotease or an active portion thereof for the manufacture of a medicament for increasing homing of stem cells to a target tissue.

Group IX: Claims 30-36, 38, and 39, drawn to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation.

Group X: Claims 30-33 and 37-39, drawn to a method of generating mesenchymal stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation.

Groups XI and XII: Claim 40, drawn to a method of generating hematopoietic (Group XI) or mesenchymal (Group XII) stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation, wherein collecting said stem cells is effected by (i) a stem cell mobilization procedure; and/or (ii) a surgical procedure, the method further comprising determining homing capabilities of said stem cells having CXCR4 levels above said predetermined threshold following step (c).

Group XIII: Claims 41, 42, 44, and 45, drawn to a nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloprotease or an active portion thereof and an inducible cis-acting regulatory element for directing expression of said polynucleotide in cells.

Group XIV: Claim 43, drawn to a nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloprotease or an active portion thereof and an inducible cis-acting regulatory element for directing expression of said polynucleotide in cells, the nucleic acid further comprising a second polynucleotide sequence being translationally fused to said first polynucleotide sequence, said second polynucleotide sequence encoding a signal peptide capable of directing secretion of said matrix metalloprotease or said active portion thereof out of said cells.

Group XV: Claim 46, drawn to a eukaryotic cell comprising the nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloprotease or an active portion thereof and an inducible cis-acting regulatory element for directing expression of said polynucleotide in cells.

Group XVI: Claims 47-52, drawn to a cell line comprising hematopoietic stem cells transformed to express an exogenous polynucleotide encoding a matrix metalloprotease.

Group XVII: Claims 47-49 and 53, drawn to a cell line comprising mesenchymal stem cells transformed to express an exogenous polynucleotide encoding a matrix metalloprotease.

Groups XVIII-XXI: Claim 54, drawn to a method of increasing sensitivity of (i) hematopoietic stem cells *in vitro* (Group XVIII) or *in vivo* (Group XIX) or (ii) mesenchymal stem cells *in vitro* (Group XX) or *in vivo* (Group XXI) to a chemoattractant, the method comprising upregulating an expression or activity of at least one endogenous MMP of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

Groups XXII and XXIII: Claims 55-57, drawn to an *in vivo* method of increasing sensitivity of hematopoietic (Group XXII) or mesenchymal (Group XXIII) stem cells to a chemoattractant in a subject in need, the method comprising administering to said patient at least one matrix metalloprotease or an active portion thereof.

Groups XXIV- XXV: Claim 58, drawn to a method of generating hematopoietic (Group XXIV) or mesenchymal (Group XXV) stem cells suitable for transplantation, the method comprising (a) collecting stem cells; and (b) exposing said stem cells to MMP or an active portion thereof.

Group XXVI: Claims 59-62, drawn to a pharmaceutical composition comprising at least one matrix metalloprotease or an active portion thereof for treating a disorder requiring cell or tissue replacement.

The Requirement for Restriction Should be Withdrawn.

The unity of claims in a national-stage application under 35 U.S.C. § 371 may be examined under 37 C.F.R. § 1.475. 37 C.F.R. § 1.499. Rule 475 provides that, even where a group of inventions is claimed in an application, the unity of invention requirement is satisfied if there is a unifying technical relationship involving "one or more of the same or corresponding special technical features." "Special technical features" are "technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art." *Id.* The Patent Office guidelines relating to double patenting rejections apply to national-phase applications submitted under 35 U.S.C. § 371. M.P.E.P. §§ 823 and 1893.03(d). In

addition, to establish a lack of unity of invention, the Examiner must explain why each group of claims lacks unity with each other group. M.P.E.P. § 1893.03(d).

The Office asserts that the claims encompass "multiple inventions, multiple methods with distinct goals and method steps . . . and multiple products . . . [that] do not have a special technical feature which links the inventions one to the other . . . ." Office Action at pages 8-9. On the contrary, a special technical feature unifying the pending claims is use of matrix metalloprotease in methods of manipulating stem cells. The Office provided no reasoning as to why the unifying technical feature assertedly does not satisfy the requirements of Rule 475. The unifying technical feature defines a contribution that the claimed subject matter makes over the prior art, and the Office has provided no reasoning or evidence to the contrary.

Moreover, the Office failed to separately address each group in its reasons for requiring restriction. According to M.P.E.P. § 1893.03(b), the Examiner must explain why *each* group lacks unity with *each other* group, specifically describing the unique special technical feature(s) of each group. The Office provided no reasoning to support the restriction among, e.g., the particular stem cell types upon which Groups I-VI, IX-XXII, and XVI-XXV are based, or methods having identical method steps, practiced *in vivo* or *in vitro*, upon which Groups I-IV and XVIII-XXI are based. The Examiner further failed to explain why, for example, the method of generating stem cells suitable for transplantation of claim 30 (Groups IX and X) is a different "invention" compared to the *same method* further comprising the step of determining homing capabilities of the stem cells, as recited in claim 40 (Groups XI and XII). At the very least, the claims of Groups IX-XII should be examined together. The particular stem cell type used in the claimed method, or the additional method step recited in claim 40, does not change the fact that the same special technical feature, defining an advance over the state of the art, is found in the claims of Groups IX-XII.

The Office also required an election of species with respect to a particular matrix metalloprotease (MMP). The Office asserted that restriction is proper in that different MMPs comprise "different amino acid sequences *rendering distinct structures and functions*" (Office Action, page 9 (emphasis added)). Yet, as noted in the instant application, members of the MMP family of enzymes have similar structure and function. As described at page 15, line 7, through page 16, line 20, MMPs are characterized by a catalytic domain of about 170 amino acids including a zinc binding motif HE*XX*H*XX*G*XX*H and a conserved methionine, which forms a

unique Met-turn structure. MMP-2 and MMP-9 further share three repeats of a fibronectin-type II domain inserted into the catalytic domain, which includes a five-stranded β-sheet, three α-helices, and bridging loops. Examples 2-4 demonstrate that MMP-2 and MMP-9 also have similar activity. MMP-2 and MMP-9 enhanced migration of human progenitor cells (Examples 2 and 4), are involved in homing to target tissue (Example 3), and are inhibited by the same compound (Examples 2-4). Thus, contrary to the Office's assertions, the entire family of MMPs, and at the very least MMP-2 and MMP-9, should be examined together.

In view of the above, the restriction requirement imposed for asserted lack of unity of invention should be withdrawn in its entirety. Alternatively, claims 30-40 (corresponding to Groups IX-XII) should be examined together without requiring a species election.

Dated: March 6, 2009

Respectfully submitted,

By _____

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